clinical reviews

Management of Cancer Therapy–Associated Oral Mucositis

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abstract

Mucositis is a common and feared complication of anticancer therapy that can affect up to 90% of certain populations of patients with cancer. Even seemingly uncomplicated mucositis, which is often self-limited, can result in intense patient discomfort and decline in quality of life. Severe mucositis can be complicated by uncontrolled pain, superinfection or systemic infection, bleeding, and dehydration, and severe mucositis can lead to interruptions or de-escalation in anticancer treatment, resulting in worse oncologic outcomes. This article provides an evidence-based summary to guide practicing oncologists in the assessment, prevention, and management of mucositis induced by chemotherapy, radiotherapy, and targeted therapy.

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INTRODUCTION

Oral mucositis is a common and feared adverse effect in patients with cancer who undergo anticancer treatment. The management of mucositis can be quite vexing for both the patient and the oncologist. Mucositis can occur throughout the GI tract, from mouth to anus, and symptoms manifest depending on the affected site.[1] Patients who develop mucositis have twice the risk of developing infections and four times the risk of death compared with patients who do not develop mucositis, and mucositis is associated with considerable financial toxicity.[1-3] Therefore, the prevention and management of therapy-related mucositis is a critical part of the oncologist's job.

A range of agents and management approaches are available to the practicing oncologist, with variable efficacy and data to support their use. In this review, we discuss the pathophysiology of mucositis; its assessment; and the approach to its prevention and management with regard to the inciting agent—chemotherapy, radiotherapy, or molecularly targeted agents. This review primarily covers the management of oral mucositis; we do not specifically cover distal GI tract mucositis, graft-versus-host disease, mucositis as the result of hematopoietic stem-cell transplantation, or antimicrobial treatment of the infectious complications of mucositis.

ASSOCIATED CONTENT

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PATHOPHYSIOLOGY AND RISK FACTORS

Historically, chemotherapy-induced mucositis has been conceptualized as a result of cytotoxic damage to rapidly dividing submucosal basal cells, resulting in epithelial cell damage, whereas radiation-induced mucositis results from damage to epithelial cells exposed to radiation.[4] More recently, the Five-Stage Model of Oral Mucositis has been proposed[4]:

1. Initiation: Radiation and/or chemotherapy induces cellular damage, which promotes reactive oxygen species formation within the basal epithelium and submucosal cells. The mucosa is grossly normal during this stage.
2. Primary damage response: Cellular damage activates p53 and nuclear factor-κB (NF-κB), which is likely the most significant event in propagating the damage response.
3. Signal amplification: NF-κB activation ultimately results in the production of the inflammatory cytokines tumor necrosis factor-α, interleukin-1β (IL-1β), and IL-6, which lead to tissue damage and cell death. During this stage, mucositis may still be subclinical or only subtly present.[4]
4. Ulceration: The result of cellular damage becomes clinically apparent; lesions in the mucosa may be apparent. During this stage, there is a high risk for bacterial colonization and the development of sepsis.
5. Healing: Healing occurs once there is cessation from ongoing tissue damage that initiated the mucositis.[4]

Newer molecularly targeted agents also carry the risk of mucositis. In the literature, targeted agent–induced mucositis is frequently referred to as stomatitis to distinguish it from the mucositis seen with chemotherapy or radiotherapy and to highlight the differences in the

mechanism of injury.[1] Numerous molecularly targeted agents are associated with mucositis; however, the risk is particularly pronounced with anti-angiogenic tyrosine kinase inhibitors (TKIs), such as sunitinib, sorafenib, axitinib, pazopanib, and cabozantinib.[5] The mechanism by which these agents cause mucositis is incompletely understood, but it has been hypothesized that mucositis results from poor healing after repeated microtrauma.[5]

ASSESSING RISK OF MUCOSITIS AND PRIMARY PREVENTION

There are several factors to consider in determining an individual patient's risk for developing mucositis, including the specific chemotherapy agent or radiation modality used and the dose, frequency, and duration of treatment. Patient factors that may influence the risk of developing mucositis and its severity include smoking, poor oral hygiene, younger age, female sex, pretreatment nutritional status, and pretreatment neutrophil counts.[6,7] In addition, genetic factors not yet fully elucidated are likely related to an individual's risk for developing mucositis.[8,9]

Before initiating any new chemotherapy that carries the risk of oral mucositis, patients should receive an oral examination to assist in risk assessment at baseline for mucositis. Patients at high risk for mucositis should be referred to dentistry for a more complete evaluation.[10] Patients should be educated in lay terms on the signs and symptoms of mucositis as well as on contingent plans and worrisome features that would necessitate emergency care.[10,11]

The risks of mucositis can be mitigated to a certain extent. Preventive measures for chemotherapy-induced mucositis include:

- Brushing with a soft toothbrush twice a day, flossing daily, and rinsing with bland solutions, such as normal saline, sodium bicarbonate, or tap water, at least four times a day are recommended.[10]
- Patients at particularly high risk may benefit from an early professional dental assessment for aggressive prophylactic care, such as treatment of caries and extraction of compromised teeth.[12,13] Aggressive prophylactic dental care reduces the risk of mucositis by $> 25\%$.[14]
- Cryotherapy or ice chip therapy, where patients hold ice chips in their mouth for 30 minutes before infusion of fluorouracil, can prevent severe mucositis.[10]
- Mucoadhesive hydrogel rinses (MuGard; AMAG Pharmaceuticals, Waltham, MA) and calcium phosphate rinses (Caphosol; EUSA Pharma, Boston, MA) can prevent mucositis, although such agents are not yet endorsed by guidelines.[15,16]

Like chemotherapy-induced mucositis, the risk of radiation-induced mucositis can be somewhat mitigated. All patients with head and neck cancer who are preparing to receive radiotherapy should be referred to a dentist before starting radiotherapy. In addition to assessing for dental caries and periodontal disease, a dental assessment can make the oncologic team aware of occult metal in the oral cavity that may affect radiation delivery or the risk of mucositis.[10] Adequate oral care, as previously described, is also important for preventing radiation-induced mucositis. In general, the radiation delivery should be optimized to limit mucosal exposure, and shielding should be used when appropriate.[10] Additional recommendations to prevent radiation-induced mucositis include:

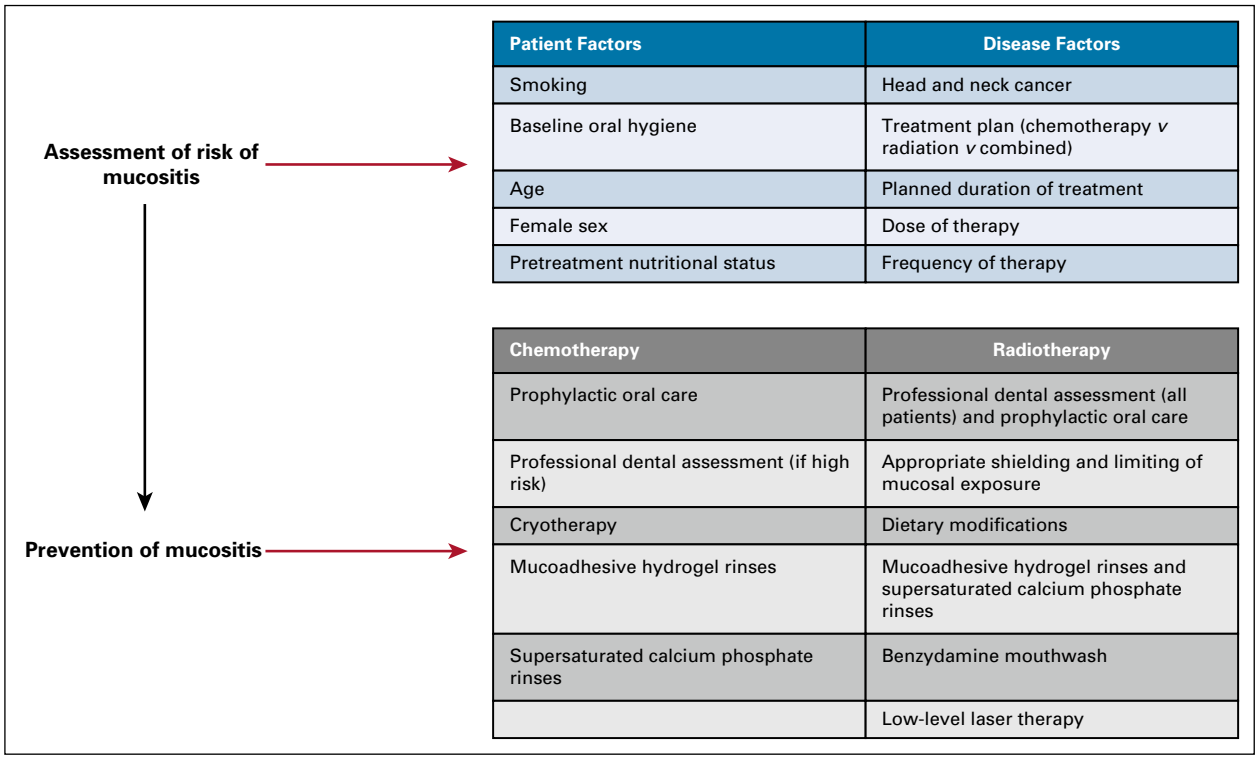
- Prophylactic dietary modifications, such as avoiding starchy, acidic, and sharp foods
- Honey, swish and spit, administered before radiation to decrease the incidence of mucositis[17]
- Mucoadhesive hydrogel rinses and calcium phosphate rinses[15,18]
- Benzydamine mouthwash for patients with head and neck cancer undergoing radiation without chemotherapy[16]
- Other interventions such as 632.8-nm laser therapy (low-level laser therapy) and zinc supplements[16,19,20]
- Prophylactic placement of a percutaneous endoscopic gastrostomy tube in patients at high risk for mucositis to prevent the onset of dehydration or weight loss.[10]

There is currently a paucity of data to guide mucositis prophylaxis for targeted agents. A combination of the approach to preventing mucositis in chemotherapy- or radiation-induced mucositis likely will be sufficient, specifically close attention to oral care.[13] For patients who receive everolimus, dexamethasone 0.5 mg/5 mL swish and spit can be used up to four times a day to prevent mucositis.[21]

ASSESSMENT OF ESTABLISHED MUCOSITIS

The approach to the patient suspected of developing mucositis begins with a thorough history and physical examination.[22,23] In particular, the patient should be assessed for level of pain; amount of tolerated oral intake; possible secondary infections (limited or disseminated); bleeding (spontaneous *v* provoked and amount); and infectious symptoms, specifically fevers (Fig 1). An oral examination also is warranted, with careful attention paid to signs of secondary infections.[16] Mucosal integrity, color, bleeding, and lesions should all be assessed.[24] A CBC with differential can help to assess for the likelihood of an infectious complication, especially if neutropenia is present. A complete metabolic panel should be obtained to assess for end-organ damage.

Mucositis severity is usually graded using the National Cancer Institute CTCAE.[24] These criteria grade adverse events from 1 through 5, with increasing severity based on clinical findings and patient symptoms[24] (Table 1). These criteria can also be adapted to mucositis as the result of targeted agents but may result in under-reporting and



Patient Factors	Disease Factors
Smoking	Head and neck cancer
Baseline oral hygiene	Treatment plan (chemotherapy *v* radiation *v* combined)
Age	Planned duration of treatment
Female sex	Dose of therapy
Pretreatment nutritional status	Frequency of therapy

Chemotherapy	Radiotherapy
Prophylactic oral care	Professional dental assessment (all patients) and prophylactic oral care
Professional dental assessment (if high risk)	Appropriate shielding and limiting of mucosal exposure
Cryotherapy	Dietary modifications
Mucoadhesive hydrogel rinses	Mucoadhesive hydrogel rinses and supersaturated calcium phosphate rinses
Supersaturated calcium phosphate rinses	Benzydamine mouthwash
	Low-level laser therapy

FIG 1. Approach to assessing risk of mucositis and prevention of oral mucositis by modality. The risk of mucositis can be assessed by patient factors and disease-related factors. The prevention of mucositis is similar between chemotherapy and radiation. No guidelines currently exist for the prevention of targeted agent mucositis; however, dexamethasone mouthwashes seem effective for preventing everolimus-induced mucositis.

inaccurate grading.[5] Other grading systems also exist and generally rely on a similar assessment of the number of lesions, the color of the mucosa, and the absence/presence of bleeding and its spontaneity.[25,26]

MANAGEMENT OF CHEMOTHERAPY-INDUCED MUCOSITIS

Mucositis occurs in 20% to 40% of patients who receive chemotherapy for solid tumors and typically occurs within 5 to 14 days of receiving chemotherapy.[16] Chemotherapy regimens containing fluorouracil, methotrexate, or etoposide are associated with a particularly increased risk of mucositis, but this can also occur in dose-dense regimens that contain other chemotherapies.[6]

Uncomplicated mucositis is generally self-limiting, and symptom management and supportive care may be all that is needed. For patients with mucositis, a reasonable approach is outlined as follows (Fig 2):

- Begin with bland rinses and topical anesthetics, such as 2% viscous lidocaine swish and spit.[27]
- Modify the diet to limit incidental trauma by avoiding rough and sharp foods (eg, potato chips).
- Avoid alcohol (in the form of beverages or alcohol-containing mouthwashes) and tobacco until symptom resolution.[11]
- Treat pain with limited risk for systemic absorption using 2% morphine mouthwash swish and spit in patients with head and neck cancer receiving chemoradiotherapy.[28]
- Consider admission to the hospital for systemic analgesics and ongoing monitoring and evaluation for secondary infections in patients with severe mucositis or who are unable to tolerate any oral intake.
- Use patient-controlled analgesia with morphine as an effective agent in reducing pain and which has good evidence to support its use in hospitalized patients.[16]

TABLE 1. Grading of Oral Mucositis by National Cancer Institute CTCAE (version 5.0)

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mucositis, oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Severe pain interfering with oral intake	Life-threatening consequences; urgent intervention needed	Death

NOTE. Adapted from National Cancer Institute.[24]

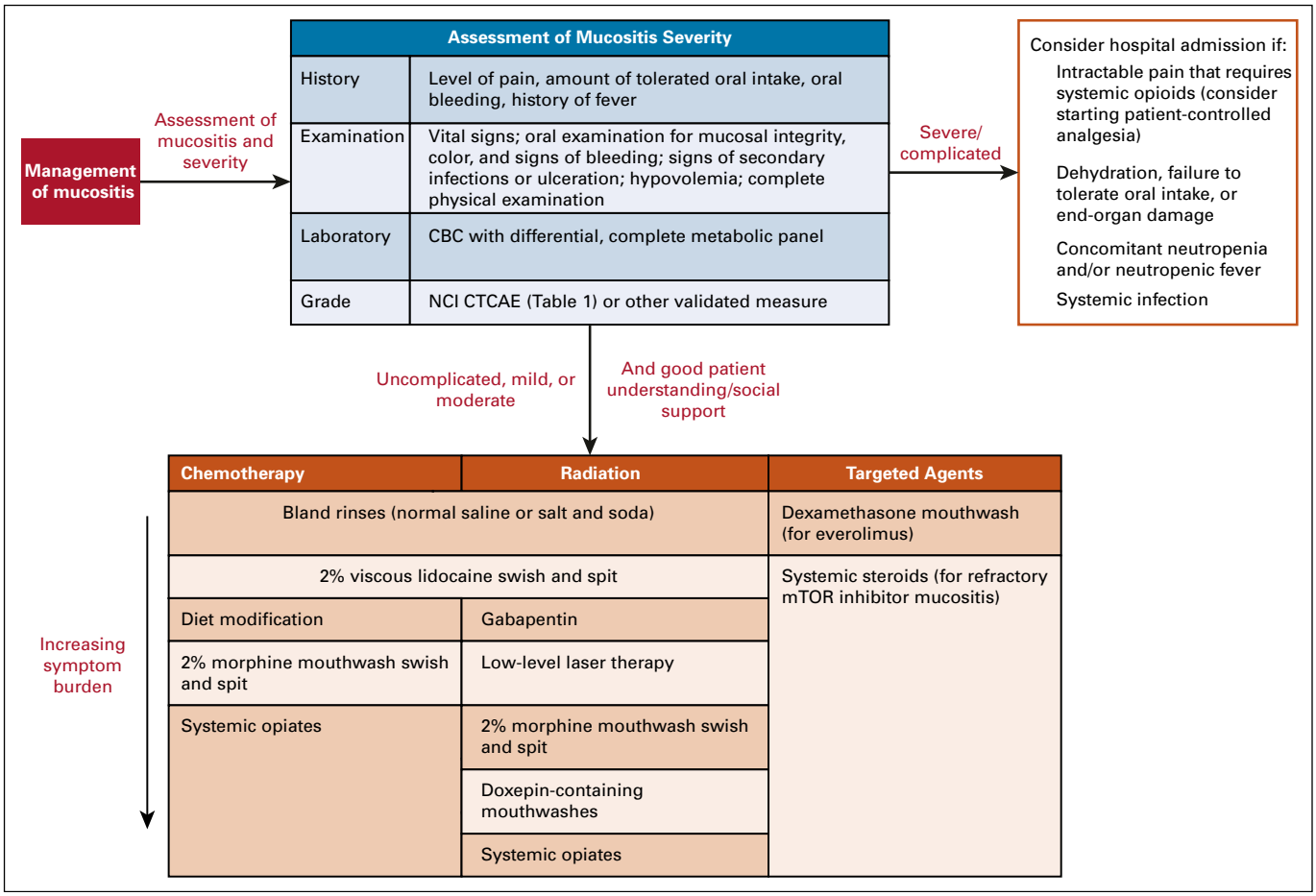


FIG 2. Approach to managing mucositis. All patients should receive a history and physical examination with a directed laboratory investigation. Uncomplicated mild or moderate oral mucositis can be managed as an outpatient. Physicians should consider admission to the hospital if the patient has evidence of hypovolemia, end-organ damage, severe pain not controlled by oral medications, or an inability to tolerate oral intake. mTOR, mammalian target of rapamycin; NCI, National Cancer Institute.

- Use transdermal formulations of morphine or fentanyl to provide long-lasting background pain control and patient-controlled analgesia to allow for management of breakthrough pain.[16]

Normal saline or sodium bicarbonate solutions can provide relief of mild to moderate mucositis pain.[10] Such salt-and-soda mouthwashes are also safe, inexpensive, and effective in treating mucositis.[22] Furthermore, patients can make a formulation of these solutions at home with 1 tsp table salt and 1 tsp baking soda in 1 pt water.[29] These mouthwashes can be performed as frequently as every 4 hours. So-called magic mouthwashes (which typically contain mixtures of topical anesthetics, antihistamines, and/or steroids) are frequently used, but these mouthwashes are neither standardized with regard to component ingredients or ratios nor more effective than bland rinses in reducing mucositis pain, and they carry the additional risk of systemic toxicity.[10,22] Viscous lidocaine solutions, swish and spit, are effective at providing topical anesthesia but can numb the entire mouth and place patients at risk for accidental trauma.[10] Chlorhexidine washes or other topical antimicrobials are not recommended for prophylaxis or treatment of mucositis except when oral hygiene is not possible. Studies of chlorhexidine have failed to show a consistent benefit compared with water placebo.[29] Sucralfate or other mucosa-coating agents are also not recommended for chemotherapy-induced mucositis.[16] Mucoadhesive hydrogel rinses and calcium phosphate rinses are also not more effective for the treatment of mucositis than placebo or standard therapy.[15,18,30]

MANAGEMENT OF RADIOTHERAPY-INDUCED ORAL MUCOSITIS

Radiation-induced mucositis occurs in up to 91% of patients with head and neck cancer who receive radiotherapy and is associated with increased use of health care resources and excessive health care costs.[23] Although its combination with chemotherapy in patients with head and neck cancer has improved outcomes, radiation-induced mucositis is often a dose-limiting toxicity, and its onset can

lead to the early discontinuation of radiotherapy with the possibility for worse outcomes.[23] Because radiation-induced mucositis is the result of tissue damage by the radiation beam, it occurs in a more predictable location and time course compared with chemotherapy-induced mucositis and typically arises in the third week of radiation.[31] However, the pain associated with radiation-induced mucositis is intense and frequently leads to interruptions in treatment.[20,31]

Clinically, radiation-induced mucositis can be managed in a similar fashion to chemotherapy-induced mucositis. A reasonable approach to treating radiation-induced mucositis is as follows (Fig 2):

- Bland rinses, such as normal saline and salt-and-soda mouthwashes, swish and spit, up to four times a day
- Topical anesthetics, such as 2% viscous lidocaine swish and spit.
- Low-level laser therapy applied to mucositis lesions to reduce the severity and duration of mucositis and which can be performed as frequently as every day[32]
- Systemic agents, including opiates[31] (morphine mouthwashes [2% morphine swish and spit]), to achieve pain control with limited systemic absorption and which may outperform magic mouthwash in reducing the severity of radiation-induced mucositis.[16,33]

Similar to chemotherapy-induced mucositis, patients who develop radiation-induced mucositis should alter their diet to limit further incidental trauma to the mucosa as a result of chewing. Spicy, rough, and sharp foods should be avoided.[34] Patients who develop radiation-induced mucositis likely will require long-acting opiates with the option for a short-acting agent for breakthrough pain until the mucositis resolves.[34] The use of gabapentin in radiation-induced mucositis may play a role in decreasing the need for opiates.[35]

Mouthwashes that contain the tricyclic antidepressant doxepin have also been trialed in radiation-induced mucositis. The Alliance trial (NCCTG-N09C6) provided initial support for the use of a doxepin rinse for reducing mouth pain from radiation-induced mucositis in patients with head and neck cancer compared with placebo.[31] A follow-up study by the same investigators, Alliance A221304, compared a doxepin mouthwash or diphenhydramine-lidocaine-antacid combination mouthwash to placebo for reducing pain in patients with head and neck cancer who underwent radiotherapy. Both treatment groups experienced identical pain relief, which was statistically significantly better than the placebo group. However, the trial failed to meet its prespecified threshold for clinical significance. Of note, patients who received the doxepin mouthwash experienced more drowsiness, unpleasant taste, and stinging or burning than those in the combination mouthwash or the placebo groups.[36] Before initiating doxepin mouthwashes, patients should be counseled on toxicity, and adverse effects should be monitored.

Topical antibiotics, sucralfate, and misoprostol are not recommended for the treatment of radiation-induced mucositis.[16] Cholinergic agents such as pilocarpine are also not recommended to treat radiation-induced mucositis but may be beneficial for symptomatic relief in patients who are also suffering from low salivary flow.[16]

TARGETED AGENTS AND MUCOSITIS

The management of TKI-induced mucositis has not been as thoroughly studied as chemotherapy- or radiation-induced mucositis. In a descriptive study of the management of adverse events related to TKIs, 29% of patients developed mucositis within 3 months of initiation, which frequently led to discontinuation, dose interruption, or dose reduction.[37] The most common treatments for TKI-induced mucositis were antifungals, mucosal protectants, antihistamines, proton-pump inhibitors, antiseptics, steroids, and analgesics. Few patients also received salt-and-soda rinses, lip moisturizers, and advice to avoid alcohol- and peroxide-containing mouthwashes.[37] No information was given to describe treatment effects in that study.

For targeted agents such as mammalian target of rapamycin (mTOR) inhibitors like everolimus, mucositis frequently contributes to dose-limiting toxicities, delays in treatment, and dose reductions.[38] Without prophylactic steroids, up to 60% of patients who receive everolimus develop mucositis, and the mucositis is distinct from chemotherapy-induced mucositis by its appearance and location, appears within 5 days of the start of the first cycle, and resolves within 1 week.[38,39] In patients who receive mTOR inhibitor therapy, dexamethasone mouthwashes are effective at reducing the incidence and severity of mucositis with minimal adverse effects.[21] In extreme cases of refractory mucositis from mTOR inhibitors, systemic treatment with high-dose steroids may be necessary.[38] Opioids are not usually necessary.[38]

Specific high-quality evidence to guide the management of patients who suffer from oral toxicity from other targeted agents, such as bevacizumab, lapatinib, and trastuzumab, is lacking.[1] Likely, a combination of oral care, topical and systemic analgesics, and dose interruption or reduction can be used.

In conclusion, mucositis is a common adverse effect of anticancer therapy and can contribute negatively to patient outcomes. The optimal management of these patients is an ongoing source of study, and an improved understanding of the pathophysiology of mucositis should inform future treatments. Regardless of the type of mucositis, patient education and communication between the patient and staff are critical to the prevention, early diagnosis, and management of mucositis.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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